

CLAIMS

1. A method of screening for agonistic antibodies that comprises the following steps (a) to (c):

5 (a) providing a cell that expresses a multimer-forming receptor and a test antibody, where the cell grow depending on a factor of the receptor;

 (b) determining the test antibody to comprise agonistic function when autocrine cell growth is autonomous; and

10 (c) selecting those antibodies that comprise agonistic function.

2. The method of claim 1 that further comprises the step of introducing a gene that encodes the heavy chain of the test antibody into the cell of step (a) having been introduced with a gene that encodes the light chain of the test antibody and a gene that encodes the receptor.

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3. The method of claim 1 or 2 where the receptor is a chimeric receptor with a protein that comprises a function of transducing a cell growth signal.

4. The method of any one of claims 1 to 3 where the receptor is a dimer-forming receptor.

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5. The method of claim 4 where the dimer-forming receptor is a homo-dimer.

6. The method of claim 4 where the dimer-forming receptor is a hetero-dimer.

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7. The method of any one of claims 1 to 6 where the protein that comprises the function of transducing a cell growth signal is a G-CSF receptor.

8. The method of any one of claims 1 to 7 that comprises the introduction of an antibody library to the cell.

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9. The method of claim 8 where the antibody library is a retroviral antibody library.

10. The method of any one of claims 1 to 9 where the test antibody is a multi-specific antibody.

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11. The method of claim 10 that comprises linking the test antibody's heavy and light chain variable regions with a linker.

12. The method of claim 11 that comprises producing the antibody with

variable regions linked by a linker, using a method that comprises the steps (a) to (c):

- (a) producing a single chain Fv against the first receptor chain;
- (b) producing a single chain antibody against the first receptor chain by linking the single chain Fv with a CH1-hinge-CH2-CH3; and
- (c) producing a multi-specific antibody that comprises the single chain antibody produced in step (b).

13. The method of claim 11 that comprises producing the antibody with its variable regions linked by a linker, using a method that comprises the steps (a) to (c):

- (a) producing a single chain Fab against the first receptor chain;
- (b) producing a single chain antibody against the first receptor chain by linking the single chain Fab with an Fc; and
- (c) producing a multi-specific antibody that comprises the single chain antibody produced in step (b).

14. A method of screening for an agonist multi-specific antibody that comprises the steps (a) to (c):

- (a) contacting between a multi-specific antibody and a receptor comprising a first receptor chain and a second receptor chain, where the multi-specific antibody comprises a variable region that can bind with the first receptor chain and a variable region that can bind with the second receptor chain;
- (b) determining whether the test multi-specific antibody comprises agonistic function; and
- (c) selecting antibodies that comprise agonistic function.

15. The method of claim 14 that comprises expressing the receptor and the test multi-specific antibody in the same cell.

16. The method of claim 15 where the cell is a cell that grows depending on a receptor factor.

17. The method of claim 15 or 16 where the receptor comprises the function of transducing a cell growth signal.

18. The method of claim 17 where the receptor is a chimeric receptor with a protein that comprises the function of transducing a cell growth signal.

19. The method of claim 18 where the protein that comprises the function of transducing a cell growth signal is a G-CSF receptor.

20. The method of any one of claims 15 to 19 where the test multi-specific antibody is determined to comprise agonistic function when autocrine cell growth is autonomous.

21. The method of any one of claims 15 to 20 that further comprises 5 the step of introducing an antibody library against the first receptor chain and the second receptor chain into the cell, respectively.

22. The method of claim 21 where the antibody library is a retroviral antibody library.

23. The method of any one of claims 14 to 22 that comprises linking 10 the light chain variable regions and heavy chain variable regions of the multi-specific antibody with a linker.

24. The method of claim 23 that comprises producing a multi-specific antibody with variable regions linked by a linker, using a method that comprises steps (a) to (c):

15 (a) producing a single chain Fv against the first receptor chain;
(b) producing a single chain antibody against the first receptor chain by linking the single chain Fv with a CH1-hinge-CH2-CH3; and
(c) producing a multi-specific antibody that comprises the single chain antibody produced in step (b).

20 25. The method of claim 23 that comprises producing the multi-specific antibody with variable regions linked by a linker, using a method that comprises steps (a) to (c):
(a) producing a single chain Fab against the first receptor chain;
(b) producing a single chain antibody against the first receptor 25 chain by linking the single chain Fab with an Fc; and
(c) producing a multi-specific antibody that comprises the single chain antibody produced in step (b).

26. The method of any one of claims 14 to 25 that comprises the introduction of "Knobs-into-holes" by amino acid substitution at the 30 multi-specific antibody CH3.

27. The method of any one of claims 14 to 26 where the multimer is a heterodimer.

28. The method of any one of claims 14 to 27 where the multi-specific antibody is a bispecific antibody.

35 29. A method for producing an agonistic antibody comprising steps (a) to (c):

(a) screening for an agonistic antibody by a method of any one of claims 1 to 28;

(b) introducing a gene that encodes the agonistic antibody selected by the screening of step (a) into a host cell;

5 (c) recovering the agonistic antibody from the host cell of step (b) or its cell culture supernatant.

30. A cell that expresses an antibody, and a receptor that multimerizes by binding with the antibody, where the cell grows depending on a factor of the receptor.

10 31. The cell of claim 30 where the receptor is a chimeric receptor with a protein that comprises the function of transducing a cell growth signal.

32. The cell of claim 30 or 31 where the antibody is a multi-specific antibody.

15 33. The cell of any one of claims 30 to 32 where the receptor that is multimerized by binding with the antibody comprises the function of transducing a cell growth signal.

34. A multi-specific agonistic antibody that comprises the linking of the light chain variable region and heavy chain variable region

20 by linkers, and the introduction of "Knobs-into-holes" by amino acid substitution at the antibody CH3.